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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/833,079	04/12/2001	Peter O'Hanley	050939-0104	1455

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EXAMINER
FORD, VANESSA L

ART UNIT	PAPER NUMBER
1645	

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17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/833,079	O'HANLEY ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *4-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 September 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-3 filed August 1, 2002 is acknowledged. Claims 4-7 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being to a non-elected invention.

The traversal is on the grounds that Groups I-III are not independent and distinct, therefore the examination of the entire application does not constitute a serious burden. These arguments have been fully considered but are not found to be persuasive for the reasons below:

The MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1) independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required.

The term "distinct" is defined to mean that two or more subjects as disclosed are related as methods of use, etc., but are capable of separate manufacture, use or sale as claimed, and are patentable over each other (see MPEP 802.01). In the instant situation, the inventions of Groups I-III are drawn to distinct inventions which are methods capable of separate manufacture, use or sale as described in the previous Office Action.

Classification of the subject matter is merely one indication of the burdensome nature of the search and the inventions are classified separately. Further, the literature search, particularly relevant in this art, is not co-extensive, for example, Group I is

drawn to a product. Groups II and III are drawn to different methods which require different method steps, parameters and endpoints. Clearly different searches and issues are involved in the examination of each Group.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Sequence Compliance

2. This application also fails to comply the requirements of 37 C.F.R. 1.821-1.825 because it contains nucleotide and protein sequences that are not identified. For example, page 8 and page 10. These unidentified sequences occur throughout the specification. Appropriate sequence identifiers should be used to comply with sequence rules. The sequences in the specification should match the sequence listing and computer readable form (CRF) submitted with the application. Correction is required.

Claim Objections

3. Claims 1-3 are objected to for the following informalities: Gal-Gal should be referred to as globoside-binding pili. The proper name of a term should be used in the first occurrence in the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vaccine using pili from Gal-Gal binding pilus-producing *E. coli* bacteria for preventing pyelonephritis, does not reasonably provide enablement for a vaccine for preventing any or all urinary tract or other microbial infections or diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 3 is drawn to a vaccine comprising dissociated pili from Gal-Gal binding pilus-producing bacteria where the said pili comprise at least one immunogenic peptide inserted into the immunodominant region of PapA that does not normally contain said peptide and a pharmaceutically acceptable carrier.

The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to a microbial infection or disease induction. The specification teaches that intravesicular BALB/c experimental model of pyelonephritis and cystitis was employed to evaluate the protective capacity of structural pilin synthetic peptide conjugate vaccines to prevent subsequent renal and/or bladder colonization by homologous piliated strain at 48 hours after bacterial inoculation (page 9).

The ability to reasonably predict the capacity of a single bacterial immunogen or combinations of immunogens to induce protective immunity from *in vitro* antibody reactivity studies is problematic. Ellis *(Vaccines, W.B. Saunders Company, 1988, Chapter 29)* exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of a protein component of a virus or microbial

pathogen that itself can elicit the production of protective antibodies"(page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an *in vitro* neutralizing antibody response fail to elicit *in vivo* protective immunity. Boslego et al (*Vaccines and Immunotherapy, Pergaman Press, 1991, Chapter 17)* teach that the etiologic agent for gonorrhea is *Neisseria gonorrhoeae* (page 211). Boslego et al teach that several vaccines have been developed against gonorrhea, for example, a single gonococcal pillin protein was used in a vaccine formulation to provide protection against gonorrhea, however, the protein fail to elicit protective immunity even though a high level of serum antibody response is induced (page 212, bottom of column 2). It is well known in the art that there are several different antigens from *Moraxella catarrhalis* (i.e. outer membrane proteins and lipooligosaccharides). It is also taught that since infections caused by *Moraxella* predominately occur on mucosal surfaces, the mucosal immune response is likely important as the first line of defense. Mucosal or surface antigen immune response would likely be important in the search for candidate vaccines Kyd et al, *(Vaccine 18 (2000), 398-406))*. It has also been recognized in the art that there is currently no vaccine to prevent Moraxella *catarrhalis* infections because of a lack of good animal models for the diseases, a lack of information about the protective antigens, a lack of *in vitro* correlates to immunity against *Moraxella catarrhalis* in humans and the pathogenic mechanisms and host immune response to the pathogens has yet to be clarified (Samukawa et al, *(The Journal of Infectious Diseases, 2000, 181:1842-5)* and Kyd et al, *(Vaccine 18 (2000), 398-406)*). While studies have been shown that the outer

membrane proteins can elicit bacterial antibodies, which promote bacterial clearance, the results have not lead to a predictable vaccine against infections caused by *Moraxella catarrhalis*. A similar situation exists with the development of lipooligosaccharides (LOS) based vaccines against infections caused by *Moraxella catarrhalis* (Gu et al, *Infection and Immunity, May 1998, p. 1891-1897).* It is well known in the art that *Plasmodium falciparum* is the etiologic agent that causes malaria. Branch et al *(Vaccine Weekly, June 8, 1998)* teach that the development of immunity against malaria parasites is a complex process and the lack of understanding of this process may have attributed to the failure of vaccine trails in naturally exposed populations (see the Abstract). Branch et al investigated the development of immunity to malaria in infants (see the Abstract). Branch et al concluded that infants and adults mounted similar anti-merozoite surface antigen –1 (MSP-1) antibody responses, however, infant responses were short-lived (see the Abstract).

The cited prior art references indicate that it would require undue experimentation to formulate and use a successful vaccine against *Neisseria gonorrhoeae, Plasmodium falciparum* or *Moraxella catarrhalis* without the prior demonstration of vaccine efficacy. The prior art cited has established that problems and barriers exist in vaccine development. The above mentioned diseases are only a few of the infections/disorders that are encompassed by the claimed invention and represent a small subset of the many diseases that exist that have no vaccine that is effective in treating and/or preventing such infectious diseases. The specification has not shown a correlation between papA or Gal-Gal binding bacteria and *Neisseria gonorrhoeae,*

Plasmodium falciparum, Moraxella catarrhalis nor has the specification shown a correlation between pap A or Gal-Gal binding bacteria and gonorrhea, malaria or infections/disease caused by *Moraxella catarrhalis*. The claimed invention broadly encompasses any microbial infection or disease caused by any microorganism. The vaccine as claimed would not provide protection against any bacteria, viruses or parasitic organism. The specification has not provided enablement for a vaccine that treats any urinary tract or any microbial infection or disease since the examples in the instant specification only teach a vaccine comprising pili from Gal-Gal binding pilus-producing *E. coli* bacteria that is protective against pyelonephritis. It would require undue experimentation by one of skill in the art to determine whether the claimed vaccines would be protective against any microbial infections or diseases other than pyelonephritis.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to developing a vaccine that

would achieve a desire level of success when administered to a patient to treat any urinary tract infection or any microbial infection or disease, 3) there are limited working examples which suggest the desired results of a successful vaccine that is to treat any microbial infection or disease since the examples in the specification that teach that the claimed vaccine is protective against disease are only directed to pyelonephritis and 4) the relative skill of those in the art is commonly recognized as quite high (post - doctoral level).

In view of all of the above, it is determined that the specification has not provided guidance that would enable one of skill in the art to be able to make and use the claimed invention commensurate in scope with the claims. One of skill in the art would require undue experimentation to determine whether the claimed vaccine can be used to protect against any urinary tract infection or any microbial infection or diseases.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-3 recite "immunodominant region of PapA". There is insufficient antecedent basis for this limitation in the claim. It is unclear as to what the applicant is referring? Is applicant referring to a foreign epitope or heterologous peptide? The metes and bounds of "immunodominant region" is not set forth. Clarification is required.

6. Claims 1-3 recite "if a corresponding protective epitope is inserted in the immunodominant region of PapA comprising an immunogenic composition as claimed in claim 1". It is unclear as to what the applicant is referring? Is the protective epitope inserted into PapA? What does it "correspond" to? Clarification is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pecha et al *(The Journal of Clinical Investigation, Volume 83, June 1989, p. 2102-2108)* in view of Steidler et al *(Journal of Bacteriology, December 1993, p. 7639-7643)* and further in view of Baga et al *(Cell, Vol. 241-251, April 24, 1987).*

Claims 1-3 are drawn to an immunogenic composition and vaccine comprising dissociated pili from a Gal-Gal binding pilus-producing bacteria, said pili comprising at least one immunogenic peptide inserted into the immunodominant region of PapA that does not normally contain said peptide and a pharmaceutically acceptable carrier.

Pecha et al teach vaccine compositions comprising homologous and heterologous pili suspended in PBS and emulsified in CFA and administered by

subcutaneously (page 2104, 2nd column). Pecha et al show that homologous or heterologous Gal-Gal pili prevent renal colonization and pyelonphritis by uropathogenic *Escherichia coli* strains (page 2104, 2nd column and Table II, page 2106). Pecha et al teach that the ability to colonize the uroepithelial mucosa is prerequisite for uropathogenic *Escherichia coli* strains to infect the urinary tract and the majority of pyelonephritogenic strains express Gal-Gal. Pecha et al also teach that the bacterial surface organelles facilitate binding to globoside present in the uroepithelium and their ability to bind to Gal-Gal moieties is not inhibited by uromodulin or the Tamm-Horfall glycoprotein (page 2107, 2nd column). Pecha et al teach that the results of their study support the concept that immunization with a bacterial surface-coat constituent can prevent mucosal infection by interfering with colonization (see the Abstract).

Pecha et al do not teach pili comprising at least one immunogenic peptide inserted into the immunodominant region of PapA.

Steidler et al teach the expression of a foreign epitope (i.e. immunoglobulin G-binding domain of protein A of *Staphylococcus aureus)* in to the papA gene of pili (i.e. carrier) in *Escherichia coli* (a Gal-Gal binding pilus-producing bacteria). Steidler et al teach the *Escherichia coli* used in the experiments were Gal-Gal binding pilus-producing bacteria because the papA operon was to obtain surface exposition of the foreign epitope. Steidler et al teach that coding sequences can be functionally incorporated in the PapA subunit of pili and can become exposed at the surface of the bacteria presumably as a part of a genuine pilus structure (page 7643, 1st column). Steidler et al teach that the presence of the mutant pap operon conferred IgG binding

capacity to the cell and in view of the compassion with the original pap operon it can be concluded that the test used in this study could distinguish between exposition at the surface of the bacteria and intracellular presence.

Pecha et al and Steidler et al as combined do not teach dissociated pili from a pilus-producing bacteria having at least one mutant that facilitates detachment of the pili from the bacteria relative to a wild-type strain.

Baga et al teach that papH was dispensable for diagalactoside-specific binding and for the formation of Pap pili (see the Abstract). Baga et al teach that the papH gene has roles in anchoring the pilus to the cell and modulating pilus length (see the Abstract). Baga et al teach papH deletion mutants that had 50%-70% of the total pilus antigen found free in the cells. Baga et al show evidence that the pap A (the gene which encodes the major pilin subunit) and papH genes are co-regulated (see the Abstract). Baga et al teach that released pilus adhesin (free pilus antigen, i.e. disassociated pili) would compete with the piliated bacteria for binding to the mucosal lining (page 248, 2nd column, and page 249, 1st column).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the vector system of Steidler et al by substituting the immunoglobulin G-binding domain of protein A of *Staphylococcus aureus* with the protective pili from a Gal-Gal binding pilus-producing bacteria of Pecha et al to be inserted into papA as taught by Steidler et al and further modifying the vector system of Steidler et al by mutating the papH gene in the pap operon as taught by Baga et al to produce disassociated pili because Baga et al show evidence that the pap A (the gene

which encodes the major pilin subunit) and papH genes are co-regulated (see the Abstract) and Baga et al teach that released pilus adhesin (free pilus antigen, i.e. disassociated pili) would compete with the piliated bacteria for binding to the mucosal lining (page 248, 2nd column, and page 249, 1st column). The immunogenic composition and vaccine of Pecha et al, Steidler et al and Baga et al as combined above would be effective against urinary tract infections (in particular pyelonephritis) because Steidler et al teach that amino acids can be functionally incorporated in the PapA subunit of pili and can become exposed at the surface of bacteria (page 7643, 1st column), Pecha et al teach that homologous and heterologous Gal-Gal pili are prevent renal colonization and pyelonphritis by uropathogenic *E. coli* (page 2104, 2nd column) and demonstrated results that support the concept that immunization with a bacterial surface-coat constituent can prevent mucosal infection by interfering with colonization (see the Abstract) and Baga et teach that released pilus adhesin (free pilus antigen, produced by a mutant in the papH gene) would compete with the piliated bacteria for binding to the mucosal lining (page 248, 2nd column, and page 249, 1st column) since Pecha et al teach that the ability to colonize the uroepithelial mucosa is prerequisite for uropathogenic *Escherichia coli* strains to infect the urinary tract.

Pertinent Prior Art

8. The prior art made of record and not relied upon is considered pertinent to applicant's *disclosure (van Die, Mol Gen Genet (1990), 222:297-303* and *Bakker et al, Microbial Pathogenesis 1990, 8:343-352).*

9. No claims are allowed.

10. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
December 6, 2002

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